

08/479,997


**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

 Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
---------------	-------------	----------------------	---------------------

08/479,997 06/07/95 ENGELHARDT

18M2/0620

 RONALD C FEDUS
ENZO BIOCHEM INC
575 FIFTH AVENUE (18TH FLOOR)
NEW YORK NY 10017

EXAMINER

HOUTTEMAN, S

ART UNIT	PAPER NUMBER
----------	--------------

1807

DATE MAILED:

06/20/96

 This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

- ☒ This application has been examined ☒ Responsive to communication filed on 6-7-95 9-18-95 11-17-95 ☐ This action is made final.

 A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133
Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|--|
| 1. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input checked="" type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input checked="" type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> _____ |

Part II SUMMARY OF ACTION

1. ☒ Claims 204 - 224 + 227 - 262 are pending in the application.
- Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-203 + 225-226 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 204 - 224 + 227 - 262 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

15. Applicant's arguments in the preliminary amendment filed 9/18/95 have been carefully considered with the following effect.

Some of applicants arguments are moot in view of the new grounds of rejection. However, the arguments that still apply are discussed below.

16. The specification is objected to for the following reasons.

A. Not all of the application numbers cited in the specification have been updated, either by inserting "now abandoned" or by replacing the number with the US Patent Number); see, for example, the application numbers on page 98 first paragraph. Updating of all of the application numbers in the specification is required.

B. A question mark appears on page 65, 11th line from the bottom of the page. Clarification and correction is required.

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. The specification is objected to under 35 U.S.C. § 112, first paragraph, because the specification, as originally filed, does not provide support for the invention as is now claimed.

Claims 207-224 and 227-262 are drawn to nucleotides having the "Sig" moiety attached to the phosphate moiety wherein the Sig moiety is limited to one of several molecular classes such as "at least three carbon atoms, a glycosidic linkage moiety, biotin, iminobiotin, ferritin, an antigen, a hapten, an antibody, etc.

Support for these claims was pointed out in original claims 125, 41, 84, 126, 129, 127 and 128. However, these claims are drawn to nucleotides in which the "Sig" moiety is attached to the base.

The only support that was found in the original disclosure was in a passage on pages 96-97 which begins "By way of summary." This passage defines "Sig" as binding to either base, sugar or phosphate and then defines "Sig" to include the particular products in the newly presented claims. However, there is no explicit description of the various claimed products bound to the phosphate anywhere in the specification. In contract, the base-linked "Sig" moieties have numerous complex chemical reactions which are necessary to synthesis the various products. These reactions include various solvents, reactants and protecting groups which are necessary so that only the base was modified and not the reactive groups on the sugar or phosphates. Thus, an explicit description of the "phosphate-Sig" reactions would have been expected in order for a skilled artisan to have reasonably concluded that the original disclosure evidenced "possession" of the currently claimed invention.

Thus, in view of the phrase "By way of summary" and the absence of any "phosphate-Sig" reactions to summarize; and in view of the complex nature of these reactions, the skilled artisan would not have reasonably expected this specification to put the artisan in possession of the invention as now claimed.

Since support for these claims was not found where pointed out nor elsewhere in the specification, these claims are considered "new matter."

19. Claims 207-224 and 227-262 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the above objection to the specification.

20. The specification is objected to under 35 U.S.C. § 112, first paragraph, for failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 204-224 and 227-262 are broadly drawn to nucleotides having various "Sig moieties" attached to the phosphate moiety.

The specification contains a sufficiently detailed disclosure, such as in Examples I-VII, to enable the construction of "sig-base" nucleotides, that is nucleotides in which the "Sig" moiety is linked to the base. It is noted that these reactions contain many specific solvents, reactants and protecting groups. This detailed disclosure enables one to obtain a reasonable product yield, a product of suitable stability for it's intended

use in nucleic acid detection assays and a product reasonably free of unwanted side products in which the Sig moiety is attached at the wrong places on the nucleotide.

However, there is no analogous disclosure for the attachment of the "Sig-phosphate" nucleotides. The broadly claimed "Sig moieties" include a very diverse population of molecules, from simple inorganic compounds like radioactive Cobalt to the complex organic molecules like enzymes. Accordingly, there are a vast number of possible chemical reaction schemes one could attempt. Without specific guidance or examples, the skilled artisan would expect that the vast majority of these reaction schemes would fail. Either the product yields would be low, the products would be too unstable or the products would be too hard to purify away from extraneous side products.

It is difficult to predict the behavior of a complex organic molecule with numerous functional groups: primary amines, carboxyl groups and alcohol groups. There is no way to establish, before the fact, which reaction conditions will result in high yields and stable products that can be purified from extraneous byproducts.

The level of skill is high in this field. Nevertheless, in view of the large scope of these claims, the lack of any guidance or specific examples, the high degree of unpredictability, the complex nature of the invention which requires both inorganic and organic chemical syntheses; it would have required undue

experimentation to enable a reasonable number of embodiments within the scope of these claims.

21. Claims 204-224 and 227-262 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 204-206, 217, 234-240, 251, 259, 261, are rejected under 35 U.S.C. § 102(b) as being anticipated by Mackey et al., Biochemistry 16(20):4478-4482, 1977 (Mackey).

Mackey teaches a radioactive signal moiety attached to the phosphorus of a nucleotide and an oligonucleotide (see for example α -[³²P]Deoxyribonucleoside 5' triphosphates and labeled DNA restriction fragments, Mackey, p.4479, col 2, starting at the first full paragraph to the end of the second paragraph on p. 4480).

24. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

25. Claims 215, 216, 221-224, 231, 233, 249, 250 and 255-258 are rejected under 35 U.S.C. § 103 for being unpatentable over Gohlke et al., US Patent 4,378,458, 3/1983, filed 3/1981 (Gohlke).

Gohlke discloses, for example, col 3, lines 3-22, the use of detection assays using labels such as fluorescent compounds, chemiluminescent compounds and enzymes like β galactosidase and, in col. 2, lines 32 and 35, antibodies.

The claims differ from Gohlke in the explicit recitation of the attachment at the phosphate moiety. However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to attach these labels at the phosphate moiety because, as explicitly stated in Gohlke, the

resulting product could be used to monitor the activity of ribonucleases (Gohlke col. 3, lines 22-35). Also, the phosphate moiety is where the other Gohlke detectable labels are attached (see Gohlke, col. 6, lines 25-51).

26. Claims 207-214, 219, 220, 227-230, 232, 241-248, 253, 254, 260 and 262 are rejected under 35 U.S.C. § 103 for being unpatentable over Gohlke in view of Sodja et al., Nucleic Acids Res, 5(2):385-401, 1978 (Sodja).

The teachings of Gohlke are explained above. Sodja teaches on page 386 the attachment, to the free 3' OH end of RNA, an avidin-ferritin label using the lysine groups of the polypeptide cytochrome-c).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the labels of Sodja in the methods of Gohlke for the expected benefit of using electron microscopic detection of the bound label.

27. Claims 218 and 252 are rejected under 35 U.S.C. § 103 as being unpatentable over Mackey in view of Roychoundhury et al., Nucleic Acids Res, 3(1):101-16, Jan 1976 (Roychoundhury).

Roychoundhury et al. teaches the labeling of nucleotides with cobalt (see for example Roychoundhury, Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a Cobalt label, in addition to the ³²P label, for the expected

Serial No. 08/479,997
Art Unit 1807

-9-

benefit of measuring an additional radioactive decay product in multiple labeling experiments. The radioactive cobalt decay product has an energy level very different from that of the ^{32}P decay product and can be measured independently of the ^{32}P decay product in experiments where ^{32}P is being used to follow another species within a reaction mix.

28. Papers relating to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Art Unit 1807. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Art Unit 1807 Fax number is (703) 305-7401.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott Houtteman whose telephone number is (703) 308-3885. The examiner can normally be reached on Tuesday-Friday from 8:30 AM - 6:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Scott Houtteman
June 16, 1996

Scott W. Houtteman
6-16-96
SCOTT W. HOUTTEMAN
PATENT EXAMINER
GROUP 1800